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10/501,028	03/14/2005	Christopher M. Starr	15021-6	1759

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EXAMINER	
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ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,028	STARR ET AL.	
	Examiner	Art Unit	
	Dr. Kailash C. Srivastava	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-29* is/are pending in the application.

4a) Of the above claim(s) *6,15 and 21-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-9,11-14 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The response and remarks filed 29 September 2008 to Office Action with Final Rejection mailed 31 July 2008 is acknowledged and entered. The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office action.

Applicants' Response-Based Withdrawn Rejections

2. In view of remarks filed 29 September 2008, the Obviousness rejection under 35 U.S.C. §103 (a) to Claims 1-5, 7-14 and 16-20 over combined teachings from Zankel et al. (US 20050026823 A1) in view of Wikepedia (Wikimedia Foundation, Inc., http://en.wikipedia.org/wiki/Sandhoff disease, Modified 2007; Printed 1/16/2008) and Jeffries et al (US Patent 5,981,194) and further in view of Neuwelt (US Patent 4,866,042) and LeBowitz (USPGPB 2003/0072761 A1) in the Office Action mailed 31 July 2008 is hereby withdrawn:

Claims Status

3. Claim 10 has been cancelled.

4. Claims 1-9 and 11-29 are pending.

5. Claims 6, 15 and 21-29 remain withdrawn.

6. Claims 1-5, 7-14 and 16-20 are under examination and are examined on merits.

Election/ Restriction

7. Regarding arguments that Claims 6 and 15 should also be considered along with Claims 1-5, 7-14 and 16-20 rather than withdrawing Claims 6 and 15 from further consideration; said withdrawal is based on applicants' election as presented in the response filed 08 November 2007, wherein an election without traverse was made to further prosecute Group I invention encompassing Claims 1-20, consisting of:

a. Claims 1-13 drawn to a method to treat a subject having a lysosomal storage disease by administering to said subject a composition comprising a p97 molecule covalently linked to a protein;

b. consisting of Claims 14-20 drawn to a p97 molecule covalently linked to a protein; and

c. additional election of following species:

i. Sandhoff disease from Claim 12; and

ii. protein- β-hexosaminidase A from Claims 13 and 20.

Accordingly, all other species mentioned in Claims 12-13 and 20 were withdrawn from further consideration. Note, each of Claims 6 and 15 is drawn specifically to α-L-iduronidase, a non-elected species. Additionally, as mentioned *supra* applicants election detailed above was without traverse and has been made Final in Office Action mailed 08 November 2007.

Since applicants have received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits, which is why each of Claims 6 and 15 remain withdrawn from consideration as being directed to a non-elected invention. See 37 CFR §1.142(b) and MPEP § 821.03.

Claim Rejections - 35 U.S.C. § 112

First Paragraph Rejection

8. Claims 1-5, 7-14 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabled (See, e.g., Examples 1-5) for:

- localization of p97 in a cell;
- preparation of p97 linked to a fluorescent marker for its detection in a cell having lysosome;
- preparation of compositions comprising p97 linked to a protein for its administration to a patient;
- potential modes (i.e., oral or other) to administer said compositions to a patient in need thereof, i.e., suffering from a lysosomal disease; and
- evaluation methods to determine the efficacy of said administration in a patient;

is not enabled for a method to treat a subject having a lysosomal storage disease comprising a method wherein a composition comprising a p97 molecule covalently linked to a protein is actually administered to said subject/patient.

The Claims are drawn to a method to treat a subject having a lysosomal storage disease comprising a method wherein a composition comprising a p97 molecule covalently linked to a protein is actually administered to said subject, wherein said subject is human, said p97 is human p97, the p97 is covalently linked to protein through a linker comprising 5-20 atoms, said linker is polyethylene glycol,

the protein is a conjugate protein, said disease is "Sandhoff disease", said protein is β- hexosaminidase A, said protein is covalently linked to soluble p97 and is a fusion protein capable of passing through the blood-brain-barrier(i.e., BBB) to enter lysosome of a cell within the central nervous system.

From the record of the present written disclosure, the claimed invention recited in Claims 1-5, 7-14 and 16-20 is not supported by the specification on record because in said specification there is no description of treating a subject having a lysosomal storage disease by administering to said subject a composition comprising p97 molecule covalently linked to a protein wherein deficiency of said protein causes said lysosomal storage disease, said protein is β-hexosaminidase A and the disease is Sandhoff disease.

A person of skill would not be able to practice the invention because undue experimentation will be required to obtain a "method to treat a subject having a lysosomal storage disease by administering to said subject a composition comprising p97 molecule covalently linked to a protein wherein deficiency of said protein causes said lysosomal storage disease, said protein is β- hexosaminidase A and the disease is Sandhoff disease.

Undue experimentation will be required due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as illustrated below.

A. Quantity of Necessary Experimentation

The specification, as currently presented does not provide any evidence on how a subject having a lysosomal storage disease is treated by administering to said subject a composition comprising p97 molecule covalently linked to a protein, wherein deficiency of said protein causes said lysosomal storage disease, said protein is β- hexosaminidase A and the disease is Sandhoff disease. The description as currently provided at pages and examples 1-5 of the specification do not show any evidence that the claimed method was actually reduced to practice according to the steps claimed in Claims 1-5 and 7-13 and further a composition comprising human p97 covalently linked to a protein (i.e., β-hexosaminidase A) was made, except for linking a fluorescent marker to a protein or a lysosome marker. The specification as currently presented does not clarify making or description of a compound comprising a p97 molecule covalently linked to a protein, wherein said protein is either β-hexosaminidase A, or one whose deficiency causes a lysosomal storage disease, or Sandhoff disease.

Thus, a person of skill will have to perform a number of permutations and combinations to practice the claimed mention invention.

B. *Limited Amount of Guidance*

The specification as currently presented does not provide a clear-cut guidance to obtain the claimed invention method/ composition according to claimed steps because the claimed method steps have not been clearly delineated in the specification for any type of treatment of a lysosomal storage disease by administering a composition comprising a protein linked to p97 through a linker, wherein p97 is a human p97, protein is a fusion protein, a β-hexosaminidase A, or is an enzyme whose deficiency causes said lysosomal storage disease. The delivery of the composition to the target site, clearance rate, degradation, the timing of delivery compared to chronological age, and other physiological factors have not been determined, let alone suggested. In short, the pharmacodynamics of any such fusion protein has not been established. The fusion protein must survive in active form to pass through the blood-brain barrier, and into the desired target cells in sufficient quantity and in sufficient timeliness to provide a treatment. Even in the examples provided, applicants have not demonstrated that any such fusion protein can be delivered to the target cell, with intact activity, and actually reduce the amount of the target storage substrate. The best that can be said is that a structurally insensitive attached fluorophore was delivered into the lysosome as determined by coextensive immunological markers.

C. *Limited Number of Working Examples in the Specification*

The specification does not provide any specific example wherein a method of alleviating a lysosomal storage disease has been reduced to practice by administering to a subject/patient in need thereof a composition comprising a fusion protein linked to an enzyme whose deficiency causes said disease and said composition comprises a protein/ enzyme linked to p97 through linker as is claimed in the instantly presented Claims 1-5, 7-14 and 16-20. (See Specification Pages 1-32 and examples 1-5.

D. *Nature of the Invention*

The currently presented specification does not delineate the claimed method /composition as is claimed in the instantly presented Claims 1-5, 7-14 and 16-20 to treat a subject having a lysosomal storage disease by administering to said subject a composition comprising p97 molecule covalently linked to a protein wherein deficiency of said protein causes said lysosomal storage disease, said protein is β-hexosaminidase A and the disease is Sandhoff disease. Thus, the method and composition claimed in currently presented Claims 1-5, 7-14 and 16-20 are unclearly/inadequately described in the specification as currently presented.

E. *State of the Prior Art*

The prior art description in the specification is adequate regarding treatment methods/compositions options currently available in the pertinent art to which the claimed invention in Claims 1-5, 7-14 and 16-20 pertains.

F. *Relative Skill Level of those in the Art*

At least a Bachelor Degree in Anatomy, Biochemical engineering, Biochemistry, Biology, Biophysics, Chemistry, Cytology, Histology, Microbiology, Molecular biology, Pharmaceutical Sciences, or Pharmacology.

G. *Predictability or Unpredictability in the Art*

Unless supported with illustrative evidence, biological responses/ phenomenon treatment methods/ compositions are unpredictable. Thus, information obtained under one set of detrimental parameters may not be extrapolated for another set of parameters/environmental or specific conditions.

H. *Breadth of the Claims*

As noted above, in item A, there are a number of claim limitations that have either not been evidenced in the specification as currently presented or addressed in the currently presented specification. Thus, the claimed invention is drawn upon claims that are not supported by the presently detailed specification.

Second Paragraph Rejections

9. Claims 9, 11 and 19 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for

failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- At Line 1 of each of the Claims 9, 11 and 19, the limitation is "conjugate". There is insufficient antecedence basis for said limitation in said claims. Claims 9 and 11 depend from Claim 1. Claim 1 does not have the limitation, "conjugate". Similarly, Claim19 depends from Claim 14, and Claim 14 also does not have the limitation, "conjugate". Appropriate correction/explanation is required.

Claim Rejections - 35 U.S.C. §103(a)

10. Claims 1-5, 7-14 and 16-20 are rejected under 35 U.S.C. §103(a) as obvious over the combined teachings from LeBowitz (USPGPB 2003/0072761 A1) and DeFrees et al. (US Patent 7,138, 371 B1) equivalent to US 20040137557 A1 (US 20040137557 A1 will be discussed in this rejection) in view of Jeffries et al (US Patent 5,981,194).

Claims are drawn to a method and a composition, wherein a composition, i.e., a conjugate, comprising soluble human p97 covalently linked to a protein by a linker of 5-20 carbon atoms is intravenously administered to a subject in need thereof to treat a lysosomal storage disease. Said conjugate passes through the blood brain barrier (i.e., BBB). In said composition, the lysosomal storage disease is Sandhoff disease and the protein is β-hexosaminidase A.

Regarding Claims 1-5, 7-14 and 16-20, LeBowitz teaches Tay-Sachs Disease is caused by deficiency in β-hexosaminidase A and further teaches compositions comprising and delivering therapeutic agents and fusion proteins comprising said material to overcome enzymatic defects associated with lysosomal storage disease (Table 1, Line10; Page 5, Column 2, Paragraphs 0057-0058; Paragraphs 0062-0063; Example 5). Please note, Tay-Sach's Disease and Sandhoff disease are GM2 gangliosidoses (Sandhoff disease, Tay-Sachs disease) related diseases caused by the deficiency of β-hexosaminidase A. LeBowitz, however, is silent regarding the material administered is a soluble p97 molecule, or a linking group linking the p97 and the protein (i.e., β-hexosaminidase A) is of 4-20 atom length or is polyethylene glycol (i.e., PEG).

DeFrees et al., disclose an embodiment in which transferrin conjugated via a linker to an enzyme, wherein said the enzyme is one that is lacking in a patient with a lysosomal storage disease (see Table 4, page 85) is administered. The patient could, for example, require said enzyme replacement therapy for that particular enzyme. The transferring in said embodiment is melanotransferrin (i.e., p97) among others

(Paragraph 1222). DeFrees et al. further exemplify that that replacement of the missing lysosomal enzyme with exogenous biologically active enzyme has been suggested to be a viable approach to treatment of lysosomal storage diseases (e.g., type I Gaucher disease, Fabry's disease, and other lysosomal storage disease) In said embodiments, the enzyme (i.e., protein) has been recombinantly prepared. Studies disclosed by DeFrees et al., indicate significantly reducing, the pathological glycolipid storage by repeated enzyme replacement by repeated intravenous injection of purified enzyme which resulted in a transient reduction in the plasma levels of the stored lipid substrate, globotriasylceramide (Paragraph, 1372, Lines1-5, 8 and 15-18). Additionally, Peptides useful to treat lysosomal storage disease can be derivatized with other targeting moieties including, but not limited to, transferrin to deliver the peptide across the blood-brain barrier The targeting moiety and therapeutic peptide are conjugated by any method discussed herein or otherwise known in the art Paragraphs 1227 and 1379-1380, for example). DeFrees et al. also teach that the peptide is linked through PEGylation and said compositions are used in treatment of Sandhoff disease caused by deficiency of hexosaminidase A and B (Table 4). Thus, DeFrees et al., teach: a method to treat a lysosomal storage disease, wherein said disease is Sandhoff disease by intravenous administering a composition comprising an enzyme/protein (polypeptide is also a protein) whose deficiency causes said disease, wherein said material is linked to p97 through a linker, the linker being a PEG (Paragraph 1120) and furthermore the enzyme is hexosaminidase A for Sandhoff disease. Additionally, DeFrees et al., elaborate the composition to be administered to treat said lysosomal storage disease.

Jeffries et al. teach a composition comprising p97 for delivering an agent across the BBB in association with a pharmaceutical carrier, wherein p97 is conjugated to the substance to be delivered in a pharmaceutical composition (Column 8, Lines 54-67) and also teach delivering said composition to the subject in need thereof to treat a lysosomal storage disease (Column 101, Line 25 to Column 102, Line 2).

One having ordinary skill in the art at the time of claimed invention would have been motivated to combine the teachings from LeBowitz with the beneficial teachings from DeFrees et al., and Jeffries et al.; because DeFrees et al., teach: a method to treat a lysosomal storage disease, wherein said disease is Sandhoff disease by intravenous administering a composition comprising an enzyme/protein (polypeptide is also a protein) whose deficiency causes said disease, wherein said material is linked to p97 through a linker, the linker being a PEG and furthermore the enzyme is hexosaminidase A for Sandhoff disease. Additionally, DeFrees et al., elaborate the composition to be administered to treat said lysosoma storage disease. Jeffries et al. expressly define a composition comprising p97 to be delivered to a subject in need of said pharmaceutical composition in treating lysosomal storage disease. The atom chain length for said

linker is within the same range of atom chain length as claimed because the prior art references teach PEG as the linker. The actual concentrations of individual components for preparation of said pharmaceutical composition may not be the same as instantly claimed. However, the adjustment of particular conventional working components/ conditions (e.g., types of complimentary materials having same physiological effects and concentrations thereof) is deemed merely a matter of judicious selection and routine optimization of a result-effective parameter, which is well within the purview of the skilled artisan. In view of the fact that the applicant's invention also recites composition comprising same components, and methods comprising the same steps and ingredients as are disclosed in prior art teachings; applicant's invention is obvious over the teachings of Examiner-cited prior art references.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify/combine the teachings from LeBowitz with the beneficial teachings from DeFrees et al., and Jeffries et al.; because DeFrees et al., teach: a method to treat a lysosomal storage disease, wherein said disease is Sandhoff disease by intravenous administering a composition comprising an enzyme/protein (polypeptide is also a protein) whose deficiency causes said disease, wherein said material is linked to p97 through a linker, the linker being a PEG and furthermore the enzyme is hexosaminidase A for Sandhoff disease. Additionally, DeFrees et al., elaborate the composition to be administered to treat said lysosomal storage disease. It is also *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." (*In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted)).

From the teachings of the references cited *supra*, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

11. No Claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached at (571)-272-0925 Monday through Thursday 7:30 A.M. to 6:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Dr. Kailash C Srivastava/
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16 October 2008

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